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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,617	GODDARD ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1005,0506*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 05/22/2006 has been entered.

Claims 6–8 and 11–17 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claims 6–8 and 11–17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants argue that the examiner's reliance on Hu is misplaced because applicants are relying on the more accurate and reliable RT-PCR method of assessing mRNA changes, as evidenced by Kuo. Applicants' arguments have been fully considered but they are not persuasive. From the evidence provided it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data. Kuo's poor correlation between microarray and proteomic expression profiles does not speak to changes in mRNA attributable to disease-independent differences between samples and does not speak to the accuracy and reliability of RT-PCR. Therefore, Applicants' reliance on Kuo is misplaced.

Applicants argue that Hu is silent regarding the reliability of pooled samples and that the examiner's concern is addressed by the first Grimaldi declaration. Applicants argue that the data in Example 18 and the first Grimaldi declaration are sufficient to establish the asserted diagnostic

utility, and the examiner has not rebutted the presumption of utility afforded Applicants' application. Applicants argue that the first Grimaldi declaration provides further facts relating to example 18, in that the DNA libraries used in the gene expression studies were made from pooled samples. Applicants argue that the PTO has not supplied any reasons or evidence to question the first Grimaldi declaration. Applicants remind the examiner that Office personnel must accept an opinion from a qualified expert. Applicants' arguments have been fully considered but they are not persuasive.

The first Grimaldi declaration has been considered. However, the MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The assertions that "Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual" (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA" (paragraph 6), "The precise levels of gene expression are irrelevant" (paragraph 7), and "If a difference is detected, ... the gene and its corresponding polypeptide ... are useful for diagnostic purposes" (paragraph 7) are conclusory and unsupported. Although the declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues, this statement is in contrast to the specification's teachings, which discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0350.

It is unknown what level of difference is being reported or how many samples were tested. The declaration does not provide anything specific concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. Given the paucity of information regarding PRO1753 mRNA expression and the complete lack of data concerning PRO1753 polypeptide expression, Hu is evidence that a skilled artisan would consider the precise level of PRO1753 gene expression as relevant.

Furthermore, the asserted diagnostic utility of the PRO1753 polypeptide depends upon its ability to differentiate normal tissue from tumor tissue. In practicing the invention some value for PRO1753 polypeptide expression must be obtained in order to make this distinction. Establishing a cutoff value for this distinction would be difficult unless one knows the degree of

variation within the pool, which Applicants have not provided. There is no evidence of record concerning the normal range of PRO1753 mRNA levels or PRO1753 polypeptide levels in normal tissue or tumor tissue. There is no evidence of record that a normal range of PRO1753 mRNA or PRO1753 polypeptide levels could be defined that would distinguish normal tissue from tumor tissue. Without a knowledge of the variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO1753 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact, the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue.

Applicants argue that the PTO argues that because there is no correlation between static mRNA and protein levels one would not know if a change in mRNA is associated with a corresponding change in protein. Applicants' arguments have been fully considered but they are not persuasive. The skilled artisan would not know if or how expression of the PRO1753 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. See Haynes (Electrophoresis. 1998 Aug;19(11):1862-71):

> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" (page 1863, right column, full paragraph 2);
>
> "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant

state of modification and/or association and their amounts." Page 1870 left column, last full paragraph;

This conclusion is supported by:

Molecular Biology of the Cell, 3rd ed. (Exhibit 7, 05/02/2005):

"other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 453, last full paragraph);

Molecular Biology of the Cell, 4th ed. (Exhibit 8, 05/02/2005):

"the final level of a properly folded protein in a cell therefore depends upon the efficiency with which each of the many steps [from DNA to protein] is performed" (page 363, last full paragraph and page 364, Figure 6-90);

Genes VI (Exhibit 9, 05/02/2005):

"production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848).

the first Polakis declaration under 37 CFR 1.132 (Exhibit 6, 05/02/2005):

"... there have been published reports of genes for which such a correlation does not exist, ..." (paragraph 6);

Meric (Mol Cancer Ther. 2002 Sep;1(11):971-9 (Exhibit 11, 05/02/2005):

Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability. Page 971, left column, first paragraph of introduction.

See also the first Polakis declaration (Exhibit 6, 05/02/2005) wherein it is taught that ~20% of the samples examined do not show a correlation between an increase in the level of mRNA and an increase in the level of the encoded protein (paragraph 5).

Applicants' analogy with gallons of gas vs. mRNA copies is acknowledged. Applicants' arguments have been fully considered but they are not persuasive. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of

corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first Polakis declaration.

Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of the expression of the PRO1753 polypeptide. In the absence of any information on the role, activity or expression of the PRO1753 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if the reported change in PRO1753 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO1753 polypeptide expression would change in cancer. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Applicants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the

statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in Brenner v. Manson:

> But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO1753 transcripts is tumor-dependent or tumor-independent and would not know if or how expression of the PRO1753 polypeptide would change in tumors. The examiner concludes that Applicants' have failed to disclose how to use the claimed invention.

The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis.

Applicants remind the examiner that Office personnel must accept an opinion from a qualified expert. However, the MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion

testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The facts to be established are whether or not the disclosed change in PRO1753 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO1753 transcripts and a corresponding change in PRO1753 polypeptides levels. The declarations do not provide any data concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. According to Dr. Polakis:

> The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. Paragraph 3.
>
> ... we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal cells. Paragraph 4.

There is no evidence of record that either the PRO1753 mRNA or the PRO1753 polypeptide is abundantly expressed in either tumor tissue or normal tissue. Given the paucity of information regarding PRO1753 mRNA expression in tumors and the evidence in the art that there are

numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO1753 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO1753 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO1753 polypeptide. Even if the examiner were to assume that the disclosed change in PRO1753 transcripts could reasonably be correlated with an assumed change in PRO1753 polypeptide expression, it still could not be ascertained if the assumed change in PRO1753 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO1753 transcripts is disease-dependent or disease-independent. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to first Polakis declaration, and 10% of the cases examined do not show a correlation, according to second Polakis declaration. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to the Polakis declarations.

Applicants cite Orntoft to support their position that changes in mRNA are generally correlated with changes in protein. Applicants' arguments have been fully considered but they are not persuasive. Orntoft (Mol Cell Proteomics. 2002 Jan;1(1):37-45) notes that it was only

possible to compare mRNA and protein alterations in relatively few cases of well focused abundant proteins (Abstract) and that in the few cases analyzed, mRNA and protein levels showed a striking correspondence although in some cases we found discrepancies that may be attributed to translational regulation, post-translational processing, protein degradation, or a combination of these (page 44, right column, full paragraph 2) and that it is at present unknown whether DNA copy number is one of the mechanisms behind alteration of these eleven proteins where they found a significant correlation between DNA copy number, mRNA expression, and protein level (page 45, left column, full paragraph 1). Furthermore, Ornfoft clearly suggest that both transcript and protein levels need to be analyzed (page 45, left column, full paragraph 2). Unlike Ornfoft, Applicants have not provided any testing of PRO1753 polypeptide expression. Plus, there is no evidence of record that either PRO1753 mRNA or PRO1753 polypeptide is abundantly expressed in either tumor tissue or normal tissue. Ornfoft does not provide any information regarding PRO1753 mRNA expression, PRO1753 polypeptide expression or the correlation between the two in tumor tissue and normal tissue. Thus, considered as a whole the evidence supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO1753 polypeptide expression changes in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. In addition, Ornfoft used gene expression and profiling techniques (microarrays and proteomics) (page 37, right column, last full paragraph) that Applicants have disparaged as inaccurate.

Applicants' additional supporting references (Exhibits 4-21, filed 05/22/2006) have been considered. However, none of this evidence discloses anything specific regarding PRO1753

mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in normal tissue and tumor tissue. The exhibits do not provide any data concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations. Regarding Orntoft and Futcher, there is no evidence of record that PRO1753 mRNA or protein is either abundantly expressed or abundantly under-expressed. Hu cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Applicants are not being asked to prove the asserted diagnostic utility either as a matter of statistical certainty or beyond a reasonable doubt. Rather, the facts to be established are, is the reported change in PRO1753 transcripts tumor-dependent or tumor-independent and, if the reported change is tumor-dependent, is there a corresponding change in PRO1753 polypeptide expression. The specification does not establish if the disclosed change in PRO1753 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Applicants have not provided any testing of PRO1753 polypeptide expression. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1753 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO1753 polypeptide, the

specification does not provide some immediate benefit to the public for the PRO1753 polypeptide and the antibodies thereto. The correlation between the disclosed change in PRO1753 mRNA and a change in PRO1753 polypeptide expression is unknown and is not disclosed. Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of the expression of the PRO1753 polypeptide.

Applicants should provide substantial evidence of a diagnostic utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan would accept without question that the reported change in PRO1753 transcripts is tumor-dependent or that the PRO1753 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO1753 transcripts. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO1753 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO1753 transcripts and PRO1753 polypeptide expression to argue that it is more likely than not that a change in PRO1753 transcripts is correlated with an assumed change in PRO1753 polypeptide expression. Without any evidence of the expression of PRO1753 in tumor tissue this argument is of no avail to Applicants. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. In view of the

countervailing evidence, Applicants' arguments, exhibits and declarations are insufficient to meet the utility requirement because they are insubstantial evidence that expression of the PRO1753 polypeptide changes in a manner that corresponds to the reported change in PRO1753 transcripts.

Claims 6–8 and 11–17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the examiner failed to make any specific findings of fact.

Applicants argue that the power to block off whole areas of scientific development is not the test for enablement.

Applicants argue that disclosure of a biological activity is not required for a skilled artisan to make or use the claimed polypeptides.

Applicants argue that disclosure of a single polypeptide cannot support a rejection for lack of enablement.

Applicants argue that the specification teaches how to make the claimed polypeptides and antibodies that bind thereto. Applicants argue that the specification provides sufficient guidance as to how to use the claimed polypeptides.

Applicants' arguments have been fully considered but they are not persuasive. All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the

> ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 110, and possessing any and/or all underlying biological activities. The level of experimentation required to make and use such an invention is clearly beyond the level of enablement provided by the specification because the specification provides no disclosure of any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110.

Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal samples is essential to Applicants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. The level of ingenuity required to make such an invention is clearly beyond that to be expected of skilled artisans. The specification does not disclose how this would be accomplished. Note that the claims are not limited to peptide fragments of the instantly disclosed SEQ ID NO: 110, as in Sutcliffe, or fusion proteins. Rather the claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 110, within the metes and bounds of the recited percent identity.

The examiner has provided sufficient evidence and reasoning to make a prima facie showing that Applicants' disclosure is not commensurate in scope with the claimed invention, which requires antibodies that "specifically detect the polypeptide of SEQ ID NO: 110."

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the examiner has not provided any reasoning or evidence as to how the absence of the disclosure of a biological activity results in a lack of written description.

Applicants argue that there is no substantial variation within the genus and that Applicants were in possession of the common attributes or features of the claimed invention.

Applicants argue that the claims are analogous to Example 14 of the written description guidelines because it was well known in the art how to make polypeptides having the recited percent identity, as evidenced by the specification at paragraphs 0256-0271, and because the specification discloses how to make antibodies that detect a particular PRO polypeptide and how to use them, as evidenced by the specification at paragraphs 0363-0379, 0407 and 0493-0499. Applicants argue that the function of producing an antibody specific to SEQ ID NO: 110 is directly related to the structure of the claimed polypeptides. Applicants argue that example 14 of the written description guidelines extends to all situations where the polypeptide is useful and there is no substantial variation within the genus. Applicants argue that claims 14-17 must share

a particular biologic activity which restricts the amount of permissible structural variation within the genus.

Applicants argue that the facts in *Wallach* are very similar to the present case. Applicants argue that the premise that a large genus cannot be described by a single species is wrong. Applicants argue that it is routine to make the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. Applicants argue that it well within the purview of skilled artisans to determine which polypeptides can be used to make the recited antibodies. Applicants argue that the predictability of this structure/function combination is sufficient to put Applicants in possession of the claimed invention.

Applicants' arguments have been fully considered but they are not persuasive.

The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 110, and possessing any and/or all underlying biological activities. However, the specification does not describe any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110.

The examiner disagrees with the premise that making the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. All nucleic acid molecules that encode a particular amino acid sequence all share the same property of encoding that amino acid sequence. The nature, type and number of nucleotide changes are discernable and predictable. However, the claimed variant polypeptides are all different polypeptides. The claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 110, within the metes and bounds of the recited percent identity. Note that the claims are not limited to fusion proteins. Unlike a biological activity, which imposes limitations on the nature, type and number of amino acid changes, the functional property of "can be used to generate an antibody ... to specially detect the polypeptide of SEQ ID NO: 110" does not limit the variation in the structure SEQ ID NO: 110 —the structure of the claimed variants — in any discernable, predictable or disclosed manner. Because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to example 14 of the written description guidelines.

Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal samples is essential to Applicants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The

obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. Therefore, skilled artisans would not recognize the disclosure of SEQ ID NO: 110 as putting Applicants in possession of the claimed genus.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
AUGUST 6, 2006